Medical and Pediatric Oncology 30:95–100 (1998)

Home Intravenous Antibiotic Treatment for Febrile Episodes in Immune-Compromised Pediatric Patients

E. Shemesh, MD, I. Yaniv, MD,* M. Drucker, MD, S. Hadad, RN, Y. Goshen, MD, J. Stein, MD, S. Ash, MD, S. Fisher, MD, and R. Zaizov, MD

The purpose of this work was to assess the feasibility of home intravenous antibiotic treatment (HIAT) for febrile episodes in immune-compromised (neutropenic, splenectomized), low-risk pediatric patients.

Thirty hematology-oncology patients who presented to our emergency room from January 1993 to January 1995 and who suffered from a febrile episode and were considered at low risk for septic complications were immediately discharged on HIAT. Patients were followed for at least 3 weeks after recovery. Patients and parents were retrospectively questioned about adverse effects and about their degree of satisfaction with home treatment. Patients who required hospitalization during this period were considered unresponsive to HIAT and were analyzed for causes and adverse effects.

Thirteen out of 60 (22%) febrile episodes, or eight out of 42 (19%) episodes of fever and neutropenia eventually led to hospitalization. *Pseudomonas* species infections were associated with the highest rate of unresponsiveness (88%). A central venous catheter infection developed in two cases following HIAT (two cases out of 640 days of therapy). No other complications were identified. No infection-related morbidity was observed. Patients and parents were highly satisfied with HIAT and wanted to use it again, if necessary.

Immediate discharge on HIAT for low-risk pediatric immune-compromised patients suffering from a febrile episode is feasible, safe, and well accepted by patients and families. Patients who are found to have *Pseudomonas* infections should probably be hospitalized. Our results are preliminary and must be confirmed by a prospective, randomized trial before definite recommendations can be made. Med. Pediatr. Oncol. 30:95–100, 1998.

Key words: immune compromised children; home IV antibiotics

INTRODUCTION

Immune-compromised children (following splenectomy or receiving chemotherapy for malignant diseases) suffering from a febrile episode are usually treated with a course of intravenous empiric broad-spectrum antibiotic therapy pending culture results[1–4]. The standard recommendation is to keep these patients hospitalized for continuous medical surveillance and reliable antibiotic delivery until the fever and, ideally, the neutropenia resolve [5–7]. Several reports have demonstrated, however, that home intravenous antibiotic therapy (HIAT) is an inexpensive and safe alterntive to long-term hospitalization [8–10]. HIAT was recently described in a pilot study of febrile and neutropenic adult patients [9]. The presumed need for initial stabilization and surveillance led the authors to suggest a mandatory initial period of a 2-day hospitalization period [9]. Defining low-risk patients for early discharge has been previously attempted [11,12] and validated [12].

The National Pediatric Hematology-Oncology Center in Israel is firmly rooted in the community and has the advantage of having an attending pediatric oncologist available around the clock for consultation with parents, patients, and emergency room personnel. According to our experience, most families are able and willing to make considerable efforts to provide their sick children with as much home care as possible. We therefore introduced a protocol whereby febrile, immune-compromised, low-risk patients presenting to the emergency room were evaluated by the attending pediatric oncologist, and if they fulfilled our criteria, were discharged on HIAT without an initial period of hospitalization.

PATIENTS AND METHODS

Study Protocol and Clinical Management

Since January 1993, all families of children under treatment at the Pediatric Hematology-Oncology Center have been informed of the possibility of home intravenous therapy for parenteral nutritional support, antibiotic administration and, recently, also chemotherapy. We present a retrospective analysis of our experience with HIAT

National Center for Pediatric Hematology/Oncology, Schneider Children's Medical Center of Israel, Beilinson Campus and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

*Correspondence to: I. Yaniv, M.D., The National Center for Pediatric Hematology-Oncology, Schneider Children's Medical Center of Israel, Beilinson Medical Campus, Petah Tiqva 49 202, Israel.

Received 28 June 1996; Accepted 1 March 1997

in 30 sick children over a 2-year period. During that time, 260 children were treated in our center. After the central venous catheter (usually Hickman type) was inserted, eligible patients and parents received instruction, under close supervision by a designated nurse, on how to administer the fluids or antibiotics. The discussion of HIAT, instruction and evaluation of competence were done as soon as possible after diagnosis, regardless of the immediate need for such therapy. Parental consent and patient eligibility for future HIAT were noted on the patients's chart.

The evaluation of a febrile, immune-compromised patient presenting to the emergency room was supervised by an attending pediatric oncologist. Standard evaluation consisted of blood cultures, complete blood count, glucose and electrolytes, urine culture and chest x-ray. Other studies were performed only when indicated by clinical findings. Eligible patients were given the initial dose of intravenous antibiotic and then discharged. The first antibiotic doses were supplied by the hospital and subsequent doses by a HIAT team (consisting of a nurse and an i.v. technician). Routine follow-up was scheduled 3 to 4 days after initiation of therapy, or earlier if needed. Parents were actively encouraged to consult the attending oncologist by phone when necessary; they also had the opportunity to consult a nurse or the HIAT team on a 24-hour basis. Patients and parents were instructed to present at the emergency room immediately should any signs of deterioration develop. It was explicitly stated that a parental desire for hospitalization was reason enough for admission.

Treatment

Intravenous broad-spectrum antibiotic therapy was prescribed for all febrile and neutropenic ($\leqslant$500 granulocytes/μL) patients and for febrile, splenectomized patients. It was also prescribed for some febrile patients at possible high risk of a serious infection (e.g., pneumonia, catheter infection) who were considered immune-compromised, although not strictly neutropenic (e.g., blast-phase leukemic patients, or patients with low and declining neutrophil counts who were not yet formally neutropenic) and in whom oral antibiotic treatment was unfeasible, unsuccessful, or inadequate. Guideline for antibiotic therapy were as follows: ceftriaxone or ceftazidime for patients with neutropenic fever; ceftazidime plus vancomycin for suspected line infection; and cefotaxime for splenectomized patients.

Intravenous treatment was discontinued 48 hours after the fever (and neutropenia, where applicable) resolved.

Hospitalization was mandated for patients with fever which lasted more than 3 consecutive days on therapy, any case of serious complication of therapy (e.g., a new catheter infection while on HIAT), whenever a deterioration in clinical status occured (e.g., mental status changes, dehydration, suspected neurological deterioration), and whenever parents or patients wished to be hospitalized. Hospitalization was strongly considered when *Pseudomonas* species were involved. In any case of a positive blood culture, the physician and the patient were informed immediately, and the patient was asked to return for reevalution and repeated blood cultures.

A follow-up visit to the Pediatric Hematology-Oncology Clinic was scheduled 2 to 3 days after discharge.

Antibiotic Regimens

Based on local bacteriological data and previous recommendations [4,13], our standard regimens were as follows:

1. Ceftriaxone (50 mg/kg/day, once a day) for fever in neutropenic low-risk patients (good clinical status, no localizing signs of infection). This regimen was previously tested in a cohort of 50 patients in our center [13].
2. Ceftazidime (100 mg/kg/day, twice daily) for febrile and neutropenic patients who appeared clinically more ''sick'' or who did not fit into the low-risk category described previously [13].
3. Ceftazidime plus vancomycin (100 mg/kg/day and 40 mg/kg/day, respectively, twice daily) for a suspected central catheter infection (with pus or exit-site swelling and redness).
4. Cefotaxime (200 mg/kg/day, twice daily) for febrile splenectomized patients.

Patient Selection

Patients eligible for immediate discharge on HIAT were required to meet the following criteria:

1. Full parental (and patient, when applicable) consent.
2. Previous demonstration of proficiency in home care (as judged by the designated nurse).
3. Less than 1 hour's travelling time from the patient's home to the nearest hospital (not necessarily our hematology-oncology center).
4. The infection was probably community-acquired (no hospitalization in the previous 48 hours).
5. No serious comorbidity existed that independently required hospitalization (as defined by Talcott et al. [9,12]); no signs of shock.
6. The underlying hematologic disease was known and presumably controlled.
7. No initial evidence of pulmonary or central nervous system infection.
8. No history of drug or child abuse in the nuclear family.
9. The patient had a functional indwelling central venous catheter.

Single-parent families, families of low socioeconomic background, and Bedouin families (who live in

TABLE I. Disease Categories

Diagnosis	No. of Patients
Acute lymphocytic leukemia	8
Beta-thalassemia, splenectomized	4
Wilms' tumor	3
Ewing's sarcoma	2
B-cell lymphoma	2
Rhabdomyosarcoma	2
Other	9

tents in the desert but have a reliable fresh water source and a refrigerator) were not excluded.

Drug Supply

Antibiotics were supplied and delivered by a commercial HIAT team of skilled personnel who instructed patients when needed, supplied ancillary equipment (e.g., gauze pads, intravenous tubing), and provided 24-hour phone support. Delivery was usually made twice a week, unless a specific need dictated more frequent visits. Support was also available on a semi-emergency basis (i.e., patients were usually able to summon the team within a few hours if some equipment failed or malfunctioned).

Patient Satisfaction

We conducted a retrospective phone survey of 24 patients and parents. The following five questions were asked:

1. Describe your degree of satisfaction with HIAT (very satisfied/satisfied/partially satisfied/not satisfied).
2. Did you feel sufficiently competent during your first experience with HIAT (fully competent/partially competent/not competent).
3. Did you notice any adverse drug effects during HIAT?
4. Was there any mechanical difficulty which eventually necessitated hospitalization?
5. If possible, would you like to use HIAT or be hospitalized during the next (hypothetical) episode?

Outcome Definitions and Follow-up

Unresponsiveness to HIAT was defined as an eventual need for hospitalization. Patients were followed for at least 3 weeks after cessation of treatment for signs of catheter infection or recurrent fever. Fever appearing during the first 48 hours following cessation of treatment was considered to represent unresponsiveness to HIAT and mandated hospitalization. A catheter infection that appeared during the 3 weeks of follow-up and had not been suspected on initiation of HIAT was considered to be the result of improper catheter care during HIAT.

RESULTS

Patient Characteristics

Overall, 30 patients (15 females and 15 males) were treated by HIAT for 60 episodes of fever over a period of two years. Median age was 8 years (range, 9 months to 19 years). The main underlying diseases are shown in Table I.

TABLE II. Bloodstream Infections: Organisms and Source

Organism	No. of episodes	Unresponsiveness to HIAT[a]	Suspected source
Staphylococcus	9	1	Catheter (6 cases) Open wound (2 cases)
Pseudomonas	7	6	Catheter (5 cases) Open wound (2 cases)
E. coli	1	–	Gastrointestinal tract
Enterobacter	1	–	–
Campylobacter	1	–	–
Streptococcus β-hemolyticus	1	–	–
Streptococcus viridans	1	–	Leg abscess

[a]Eventually needed hospitalization.

Characteristics of Infections

Blood cultures were positive in 21 febrile episodes (31% of all episodes, Table II).

Clinical presentation consisted of: (1) fever without an obvious source of infection and neutropenia (42 cases, 70%); (2) presumed central venous catheter infection (12 cases, 20%; Six in neutropenic patients); (3) fever in splenectomized patients (four cases, 7%); and (4) fever unresponsive to oral antibiotics (two cases, both were eventually confirmed as pneumonia and the patients hospitalized).

Characteristics of Home Therapy

A mean of 10.6 days of HIAT were necessary per episode (range, 1 to 24 treatment days), group total 640 days. Treatment duration for each regimen is shown in Table III.

Patients were examined by their oncologist during home therapy for a mean of one visit per 2.9 days on HIAT (group total, 219 office visits).

Treatment Outcome

A total of 13 cases (22%) led to hospitalization (unresponsive cases, Table IV) during or shortly after HIAT: in seven of these (88%), the source of infection was *Pseudomonas* species.

Of the 42 episodes of fever without an obvious source of infection and neutropenia, eight (19%) eventually led to hospitalization. Two of these patients suffered from a catheter infection, four were eventually positive for *Pseudomonas* in serial blood cultures (three of the four were hospitalized *before* culture results were known because of unremitting fever), one suffered from sinusitis,

TABLE III. Antibiotic Regimens and Duration of Treatment

Antibiotic	Treatment days (total)	Average duration of treatment per episode in days (range)	No. of episodes
Ceftriaxone	412	10.3 (1–17)	40
Ceftazidime	123	12.3 (2–24)	10
Ceftazidime plus vancomycin	67	11.2 (2–22)	6
Cefotaxime	38	9.5 (7–14)	4

TABLE IV. Unresponsive Cases (Eventually Needing Hospitalization)

Diagnosis	No. of cases
Confirmed *Pseudomonas* infection (positive blood culture)	6
Pseudomonas wound infection	1
Catheter infection	2
Pneumonia	2
Sinusitis	1
Intractable vomiting	1

and one from intractable vomiting. They all recoverd after a mean stay of 8 days in the hospital.

Five out of 12 patients who were *not* neutropenic were eventually hospitalized (41.6%). Of the 12 cases of suspected central catheter infection, only two (17%) led to hospitalization. One patient eventually required the removal of the central catheter.

In all, unresponsive patients were hospitalized for a mean period of 21 days (range, 14 to 36 days). All cases recovered with no obvious sequelae. Two patients required eventual removal of central venous catheter, one on an out-patient basis. Although six patients died during this 2-year period, none of them did so within 3 months of HIAT, and all deaths were clearly associated with disease progression.

Complications of Treatment

Central catheter infections developed in 2 patients following HIAT (two cases per 640 treatment days, a risk of 0.3% per day, or two of 60 cases, a 3% risk per case). These patients were hospitalized, but it was not necessary to remove the catheters.

No serious adverse drug reactions were observed during HIAT. One episode of intractable vomiting mandated hospitalization, but was probably related to chemotherapy and not to the antibiotic used (ceftriaxone in this case). No adverse reactions were detected on the follow-up questionnaire.

Antibiotic Regimens and Outcome (Table III)

Forty cases of fever were initially atreated with ceftriaxone. Nine of these (23%) eventually led to hospitalization, four for *Pseudomonas* infections. Four of six cases who received a combination of ceftazidime and vancomycin (67%) were eventually hospitalized, two because of resistant *Pseudomonas* infection and two because of resistant catheter infection. Of the 10 cases who received ceftazidime alone, none required hospitalization. None of the splenectomized cases, who received cefotaxime, needed hospitalization.

Patient Satisfaction

All 24 parents and patients surveyed were very satisfied with HIAT and wanted to use it at the next hypothetical episode. Five of the 24 felt only partially competent at the first episode and needed expert help. No one noted a specific adverse drug reaction, but five patients cited fatigue as a common problem during therapy. None encountered serious mechanical problems.

DISCUSSION

We report a pilot of HIAT for 30 immune-compromised (mostly neutropenic) pediatric patients who presented at the emergency room with fever and were immediately discharged following an initial work-up. To the best of our knowledge, this is the first report exploring the adequacy of HIAT without a stabilization period in such a population.

Our very restrictive selection criteria were based on those suggested by Talcott et al. [9,12] for adult neutropenic patients, but with several added requirements: the patient had to have a functional central venous catheter; an attending pediatric oncologist had to be available 24 hours a day for decisions regarding hospitalization *and* to answer questions of parents and children; parental concern alone mandated hospitalization; a follow-up visit was immediately scheduled upon discharge; continuous fever of more than 3 days' duration on HIAT mandated hospitalization. It is possible that some of these requirements were actually superfluous.

Our definition of unresponsiveness to HIAT (hospitalization required for *any* reason) was deliberately very broad. We may have hospitalized more patients than we really needed to (e.g., some patients with pneumonia or with persistent fever would have fared at least as well at home). Nevertheless, our unresponsiveness rates compared favorably with those of Talcott et al. [9].

The higher hospitalization rate for our patients who were not neutropenic compared to the rate for those who were (41.6 vs. 19%) can be attributed to patient selection: only patients who were judged to have relatively serious infections were considered for HIAT, if they were not neutropenic.

We were able to identify a causative organism in 31% of the blood cultures. This relatively high percentage suggests that although our criteria probably excluded the most seriously ill patients, a significant proportion of the

remainder still suffered from confirmed bacteremia. The high prevalence of staphylococcal infections probably reflects our inclusion criterion of an indwelling central venous catheter.

The association between a confirmed *Pseudomonas* infection and unresponsiveness to HIAT (88%) is not surprising. *Pseudomonas* species are relatively resistant to antimicrobial therapy, and modifications of the initial treatment are frequently required in affected patients. We strongly recommend very cautious treatment of suspected or confirmed *Pseudomonas* infections, and probably hospitalization. Our rate of *Pseudomonas* infections compares with those reported for a larger Israeli pediatric population [14,15]. A suspected catheter infection was associated with a need for hospitalization in only 16% of cases. A suspected catheter infection should not, therefore, preclude the use of HIAT.

Ceftriaxone was associated with a slightly higher percentage of hospitalization (23%), although it was used for presumably milder cases. The initial use of ceftazidime might have resulted in less need for in-patient treatment, although a previous report [13] has suggested that ceftriaxone might be sufficient for certain low-risk patients. The very high rate of hospitalization for patients who received ceftazidime plus vancomycin as initial treatment (67%) probably reflects the fact that this regimen was used only for highly suspected serious catheter infections. In this subgroup (i.e., initial clear evidence of exit-site infection or severe tunnelitis), it is probably advisable to hospitalize immediately.

Complications of treatment were rare. There were no catastrophic events (e.g., fluid overload at home). Catheter infection developed in two cases (3%), or 3.1 infections per 1,000 days of treatment. Previous studies [16,17] have reported a risk of 2.9 and 2.54 catheter complications per 1,000 treatment days, respectively, in hospitalized patients. We believe that parental mishandling of the catheter was not a significant risk factor for catheter infections in our group.

Parental satisfaction was almost complete. Some parents indicated they were a bit uncomfortable and insecure on the first days of home treatment. Our ongoing experience suggests that it might prove useful to send a nurse for one home visit during the first days of treatment.

We did not tackle the issue of the economic outcome of HIAT, although others have commented on the significant savings incurred by this method of treatment [8–10,18–20]. Although HIAT is cheaper than hospitalization, we are not sure whether it will prove beneficial to hospitals which are funded solely on the basis of hospitalization days. Nevertheless, even if the economic gain is controversial or hard to calculate, we believe patient satisfaction is reason enough to support HIAT.

In conclusion, we believe our results clearly show that immediate discharge on HIAT is feasible and safe for a preselected immune-compromised pediatric population. No pilot study can safely recommend one method of treatment over another, and ours is no exception. A randomized, controlled, prospective trial is needed to reach valid conclusions on home therapy with hospitalization. We hope our experience will make such a trial feasible and contribute to the already expanding indications for HIAT.

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